

Long-Term Benefits of Aggressive Treatment for Primary Colorectal Cancer

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The long-term follow up of 128 colorectal cancer patients is reported. Seventy-nine percent (101/128) of the patients had curative resections: 70 patients had radical lymphadenectomies with wide removal of tumor-adjacent nodes, and 31 patients had standard resections. The 5-year overall survival rates for Dukes' stage B and C patients and for all rectosigmoid cancer patients significantly favored radical resection (60% vs. 38%, 57% vs. 29%, respectively, $P < 0.05$). Tumor-free survival rates were also higher after radical lymphadenectomy but did not reach statistical significance. Eleven percent (14/128) of the patients required multiorgan resections, and/or preoperative radiation to render fixed cancers resectable, and these patients had a 10-year tumor-free survival rate of 45%, compared to zero % 5-year survival for the 27 patients who underwent palliative procedures ($P < 0.01$). These results confirm that many colorectal cancer patients will be cured with aggressive treatment and they support the need for a controlled trial for evaluation of lymphadenectomy for this disease.

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KEY WORDS: lymphadenectomy, radical surgery, colorectal cancer

INTRODUCTION

The term "radical surgery" for colorectal cancer has been used for several different operative techniques, some of which are of proven value whereas others remain controversial. For example, 10–64% of the patients who have en bloc resection of colorectal primaries invading adjacent organs, resection of anastomotic recurrences, and removal of liver metastases have been long-term survivors [1–7]; this clearly shows the benefit of such procedures. It is not as certain, however, whether preoperative radiotherapy intended to make "fixed" colorectal cancers resectable [7–14], and the wide removal of tumor-adjacent lymph nodes [5,15–41] really increase long-term patient survival. In addition, the therapeutic value of placing a "high tie" on the inferior mesenteric artery and performing radical aortic lymphadenectomies for mid- and low rectal cancers has been questioned [24,35,37,38].

We now report the results for 128 consecutive colorectal cancer patients treated over an 8-yr period at a single institution by two surgeons. One of these surgeons

routinely performed a "radical resection," which involved the removal of as much tumor-adjacent mesentery as possible, whereas the other removed only tumor-adjacent mesentery that was easily mobilized. Eleven percent (14/128) of the patients also required multiorgan resections of their primary tumors and, in some cases, preoperative radiation for a curative operation.

We found that the wide removal of tumor-adjacent mesentery during resections of primary colorectal cancer resection *may* lead to increased patient survival, although differences in patient selection may explain these results. Most importantly, we found that an aggressive approach to rendering colorectal cancer patients tumor-free at the time of treatment of the primary cancer, including preoperative radiation therapy to make "fixed" colorectal can-

Accepted for publication March 26, 1996.

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cers resectable, leads to cure of patients who would otherwise be lost to progressive disease.

MATERIALS AND METHODS

The clinical outcomes of 128 consecutive male patients with colorectal cancers treated by two attending surgeons at the Albuquerque Veterans Administration Medical Center between July 1, 1978, and June 30, 1986, form the basis of this report. Follow-up was complete for 98% (125/128) of the patients and averaged 131 months (range, 78–184 months) for survivors: 2 patients with Duke's stage A carcinomas were lost to follow-up at 20 and 65 months after resection, and 1 patient was lost 12 months after resection of an anastomotic recurrence. The average age of the patients was 65 yrs (range, 31–91 years). The ages of 31 patients who had single cancers treated by standard resection averaged 69 yrs (range, 46–88 years), compared to 63 years (range, 39–88 years) for the 56 patients with single cancers treated by radical resection. The 38 patients with rectosigmoid cancers treated by radical resection averaged 65 years of age (range, 47–88 years), as did the 17 rectosigmoid cancer patients treated by standard resection (range, 46–77 years).

The 27 patients found to have diffuse metastatic disease at initial laparotomy had either palliative resections or bypasses performed. Patients without metastatic disease whose tumors were nonresectable because of fixation to retroperitoneal structures had their tumors marked with clips, followed by abdominal closure, and a 1-month course of external-beam radiation therapy. After an additional month of rest following the radiotherapy, these patients were re-explored, and an attempt was made at curative resection. Patients without metastatic disease whose tumors were invading resectable structures had en bloc curative resections performed, and one patient had two synchronous liver metastases removed at the time of primary resection.

Patients were assigned to one of the two attending surgeons according to the referring physician's preference. One attending surgeon routinely performed a "standard" resection and the other a "radical" resection for potentially curable lesions. Only tumor-adjacent mesentery which could easily be mobilized was taken during the standard right and transverse colectomies. For standard left colectomies, the mesenteric dissection was usually carried to the division of the left colic and superior hemorrhoidal vessels. For rectosigmoid cancers, the standard resections were carried through the sigmoid mesentery and mesorectum without formal removal of all the nodes over the aorta, aortic bifurcation, sacrum, and internal iliac vessels.

For the radical right and transverse colectomies, all of the colonic mesentery between the superior mesenteric vessels and the colon was removed. The inferior mesenteric artery was tied flush with the aorta, and formal aortic node dissections were performed in radical resection of

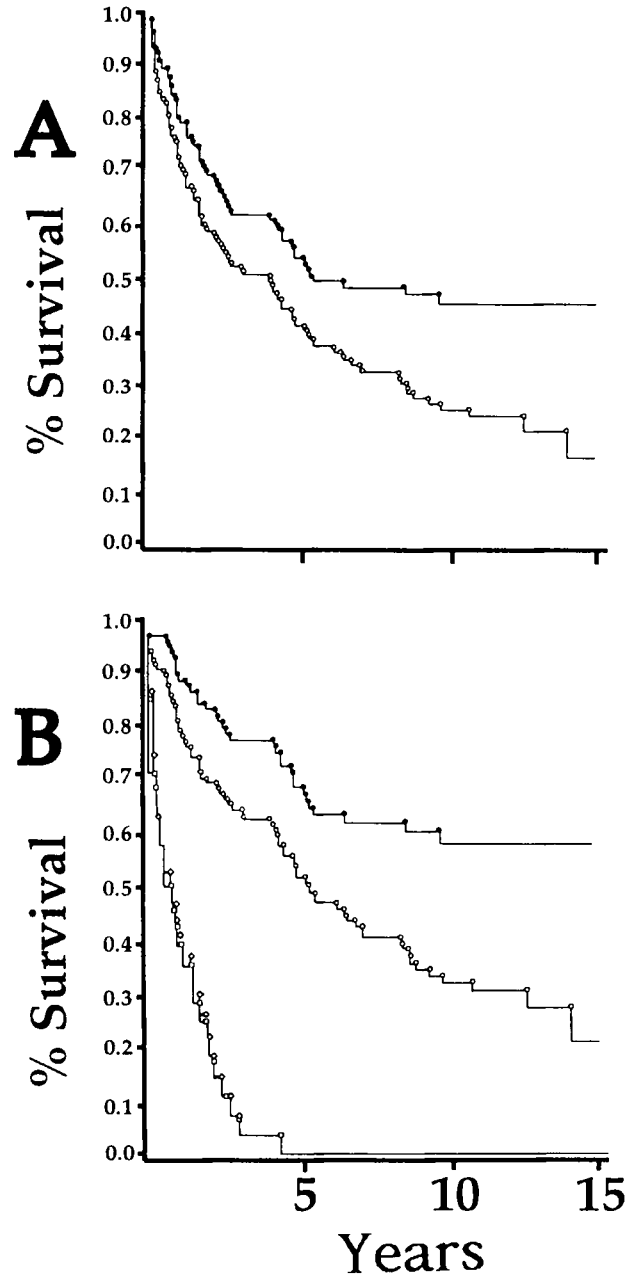


Fig. 1. Overall and tumor-free survivals of the entire series (A) and after palliative and curative resections (B). A: Entire series of 128 patients: ●—●, tumor-free survival; ○—○, overall survival. B: Curative resection (101 patients): ●—●, tumor-free survival; ○—○, overall survival. Palliative operation (27 patients): —□—□, overall survival.

cancers of the descending colon. The radical rectosigmoid resections involved removal of the entire mesentery over the aortic bifurcation and sacral promontory, and, for lower rectosigmoid lesions, this dissection was carried posteriorly onto the sacrum and out laterally, with bilateral internal iliac node dissections carried down the pelvic side walls. Obturator node dissections were not carried out. Although the inferior mesenteric artery was often tied flush to the aorta to allow mobilization of the left

TABLE I. Survival Data

	No. of patients	5-yr survival (%)	5-yr survival (P)	10-yr survival (%)	10-yr survival (P)
Entire series					
Overall survival	128	42	NA	25	NA
Tumor-free survival	128	54		45	
Curative vs. palliative resection					
Overall survival					
Curative resection	101	53	<0.01	32	<0.01
Palliative operation	27	0		0	
Tumor-free survival					
Curative resection	101	70	<0.01	58	<0.01
Palliative operation	27	0		0	
Dukes' stage B and C patients					
Overall survival					
Radical resection	53	60	<0.04	38	0.09
Standard resection	26	38		25	
Tumor-free survival					
Radical resection	53	77	<0.24	63	0.40
Standard resection	26	60		54	
Rectosigmoid cancers					
Overall survival					
Radical resection	38	57	<0.03	32	.05
Standard resection	17	29		0	
Tumor-free survival					
Radical resection	38	74	<0.17	58	0.09
Standard resection	17	50		0	
Aggressive resection versus palliative operation					
Overall survival					
Aggressive resection	14	39	<0.01	23	<0.01
Palliative operation	27	0		0	
Tumor-free survival					
Aggressive resection	14	45	<0.01	45	<0.01
Palliative operation	27	0		0	

colon, formal aortocaval lymphadenectomies starting from the duodenum over the aortic bifurcation were not carried out for mid- and low rectal lesions. Radical antero-posterior resections combined removal of the posterior sacral/coccygeal fat pad, internal iliac, and pelvic side wall dissections, with a wide resection of the levator ani muscles and ischial rectal tissues.

During the radical resections, the distal and proximal bowel were occluded with constrictive tapes or, for rectal lesions, the anus was sutured closed in an attempt to prevent in-transit metastases from intraluminal cancer cells. Also, in the radical resections, the tumor-bearing segment of the colon was devascularized as much as possible prior to its manipulation.

Survival curves for each tumor stage were constructed according to the Kaplan-Meier method [42-44], and each survival curve was compared with a log-rank test by use of "SAS lifetest procedure" software (SAS Institute, Cary, NC). The cancers were stage pathologically according to the Astler-Coller modification of the Dukes' staging system [45,46].

RESULTS

The hospital mortality for the 70 patients who underwent radical resection was 4% (3/70), with all deaths due to perioperative myocardial infarctions. Thirteen percent (4/31) of the 31 patients who underwent nonradical resections died in the hospital, 1 due to a cerebrovascular accident, 1 due to pneumonia, 1 from gastrointestinal bleeding, and 1 from an intra-abdominal abscess. The hospital mortality was 33% (9/27) for the 27 patients who underwent palliative operations. Although all these latter deaths were at least in part attributable to rapidly progressing cancer, there were three surgical complications, including one myocardial infarction, one gastrointestinal hemorrhage, and one intra-abdominal abscess.

The 5- and 10-year overall survival rates of all patients were 42% and 25%, with 5- and 10-year tumor-free survival rates of 54% and 45% (Fig. 1A). Seventy-nine percent (101/128) of the patients had curative resections, and the overall 5- and 10-year survivals of these patients were 53% and 32%, with 5- and 10-yr tumor-free survival

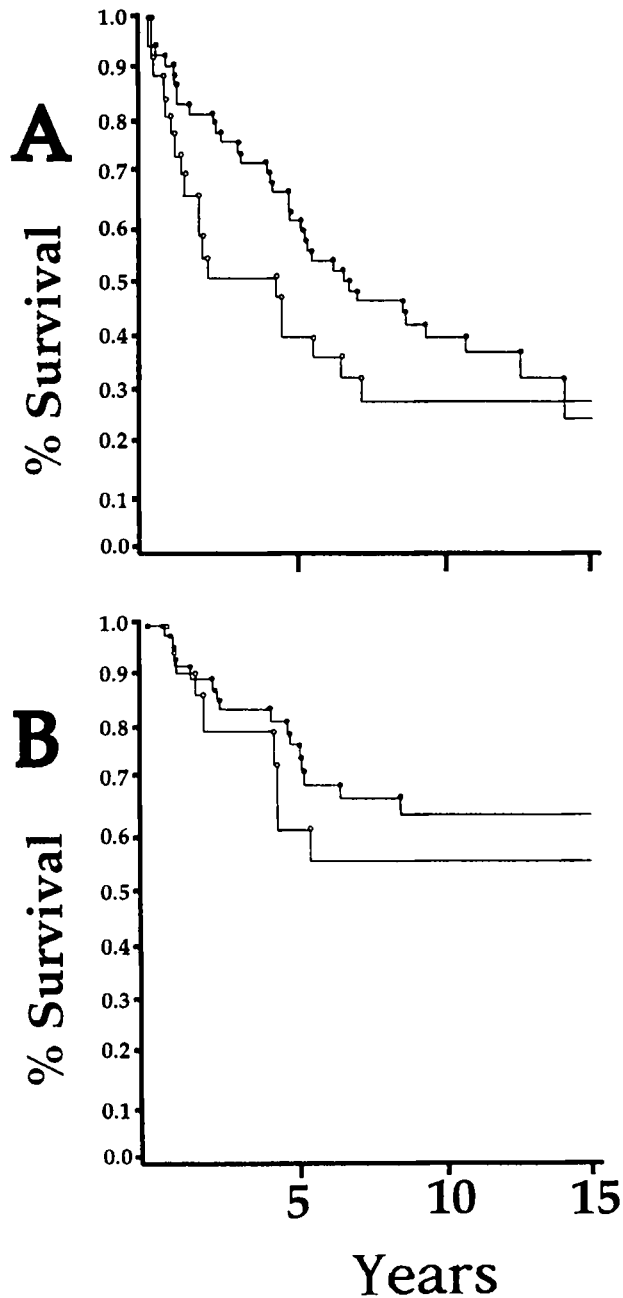


Fig. 2. Overall (A) and tumor-free survivals (B) of Duke's stage B and C patients who underwent radical (53 patients) and standard (26 patients) curative resections. ●—●—●, radical resection; —□—□—□, standard resection.

als of 70% and 58%, respectively (Fig. 1B). By contrast, none of the patients who underwent palliative procedures survived for 5 years ($P < 0.01$) (Fig. 1B, Table I).

Sixty-eight percent (87/128) of the patients had curative resections of single cancers not invading other organs, and the Duke's staging of these cancers correlated with long-term patient survival (data not shown): 9% (8/87) were Duke's stage A; 60% (52/87) were Duke's stage B; and 31% (27/87) were Duke's stage C. There was only

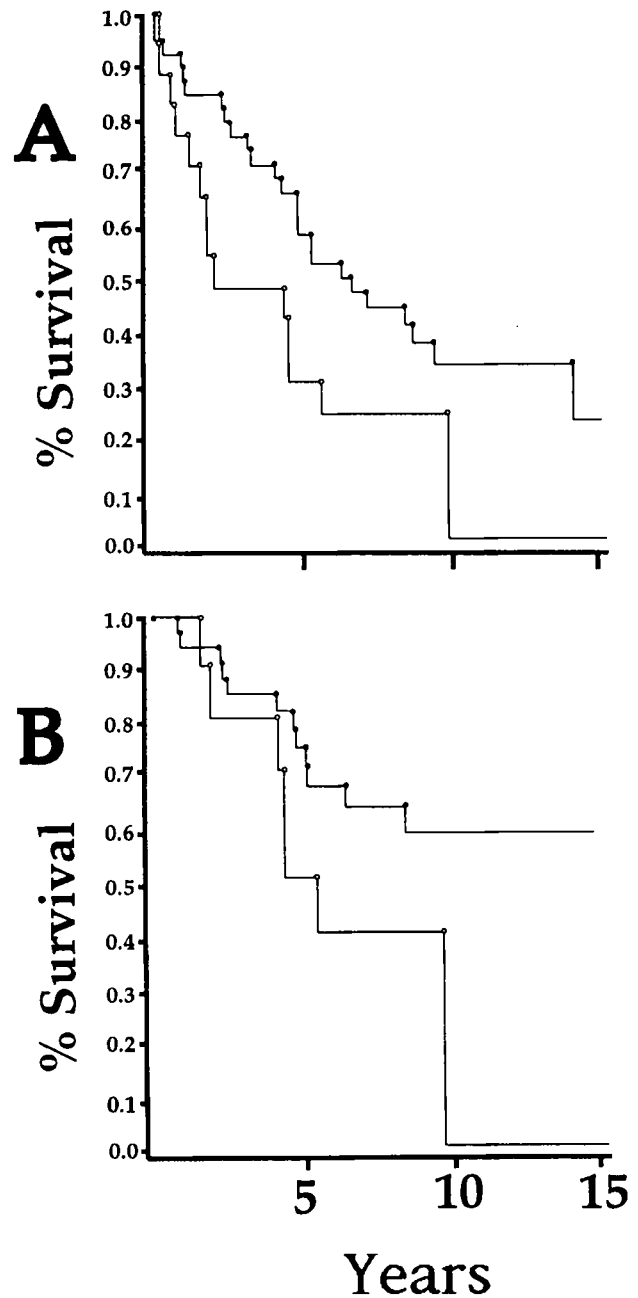


Fig. 3. Overall (A) and tumor-free survivals (B) of rectosigmoid cancer patients who underwent radical (38 patients) and standard (17 patients) curative resections. ●—●—●, radical resection; —□—□—□, standard resection.

1 tumor death among the 11 patients with Duke's stage A cancers, which occurred in the standard resection group. Of the 26 patients with Duke's stage B and C cancers who underwent standard resection, 62% (16/26) were Duke's stage B and 38% (10/26) were Duke's stage C, compared to 68% (36/53) stage B and 32% (17/53) stage C for the 53 patients who underwent radical resection (p : NS). The 5- and 10-year overall survival rates for the radically resected stage B and C patients were

TABLE II. Patients for Whom an Aggressive Attempt Was Made to Obtain a Curative Resection

Case No.	Primary	Radiation	Response to radiation	Organs resected in addition to colon or rectum	Survival (mo)	Tumor death
1	Rectal	2326 R, π meson	No	Palliative, tumor left behind	2	Yes
2	Rectal	3,000 R, π meson	No	Palliative; tumor left behind	9	Yes
3	Rectosigmoid	4,500 R, external-beam photon	Yes	Bladder	148	Alive
4	Rectosigmoid	3,500 R, external-beam photon	Yes	Bladder	52	No
5	Rectosigmoid	4,600 R, external-beam photon	Yes	Bladder	59	Yes
6	Cecal	4,600 R, external-beam photon	Yes	Curative, rt colon and cecum only	15	Yes
7	Rectal	No	NA	Bladder	8	Yes
8	Sigmoid	No	NA	Ureter	33	Yes
9	Sigmoid	No	NA	Anastomotic recurrence	120	Alive
10	Splenic Flexure	No	NA	Anastomotic recurrence	12	Lost
11	Splenic Flexure	No	NA	Stomach, spleen, pancreas	11	Yes
12	Splenic Flexure	No	NA	Spleen	31	Yes
13	Rectum, sigmoid, rt colon	No	NA	3 synchronous primaries	20	Yes
14	Transverse colon	No	NA	Stomach	102	No
15	Transverse colon	No	NA	Abdominal wall	108	No
16	Transverse colon	No	NA	2 liver metastases	171	Alive

60% and 38%, respectively, compared to 38% and 25% for the patients who had undergone standard resections (Fig. 2A). The 5-year overall survivals significantly favored the radical operation ($P < 0.04$) (Table I), although at 10 yrs the p value was only 0.09 (Table I). When tumor deaths alone were considered for the stage B and C patients, however, the 5- and 10-year survival rates after radical resection were 77% and 63%, respectively, compared to 60 and 54% after standard resection (Fig. 2B). These tumor-free survival data were not significantly different between the two procedures at either time period (Table I).

The amount of tumor-adjacent, lymph node-bearing tissues removed by the radical resection technique employed in this series differed the most from that removed by standard resection for lower-sigmoid and high- and mid-rectal cancers (see Materials and Methods). The Dukes' stages of the 17 rectosigmoid cancers from the patients who underwent standard resection were 24% (4/17) stage A, 41% (7/17) stage B, and 35% (6/17) stage C, compared to 5% (2/38) stage A, 66% (25/38) stage B, and 29% (11/38) stage C for the 38 radically resected rectosigmoid cancers. The 5- and 10-year overall survival rates for the rectosigmoid cancer patients treated by radical resection were 57% and 32%, respectively, compared to 29 and 0% after standard resection ($P < 0.05$) (Fig. 3A, Table I). The tumor-free survival rates of the rectosigmoid

cancer patients treated by radical resection, compared to those of patients treated by standard resection, were 74% vs. 50% at 5 years ($P < 0.17$) and 58% vs. 0% at 10 years ($P = 0.09$) (Fig. 3B, Table I).

Eleven percent (14/128) of the patients required an aggressive approach for a curative resection (Table II). Five rectosigmoid cancers and 1 cecal cancer (see Case Report) were found to be nonresectable at initial exploration because of fixation to retroperitoneal structures. These patients were closed, given external-beam radiation, and then re-explored with an attempt made at curative resection. Two of these cancers were treated with 2,326 and 3,000 R of π -meson radiation without an appreciable tumor response, forcing the performance of palliative resections through residual tumor (Table II). The other four cancers became mobile, having previously been fixed to retroperitoneal structures, in response to 3,500 to 4,600 R of external-beam photon radiation therapy, allowing the performance of potentially curative resections (Table II).

Six additional patients required en bloc resections at primary operation, without preoperative radiation, of cancers invading adjacent structures. Finally, two other patients had radical reresections of anastomotic recurrent cancers that had been resected previously in a standard manner; one patient had two synchronous liver metastases removed at primary operation; and one patient required the resection of 3 synchronous primaries (Table II).

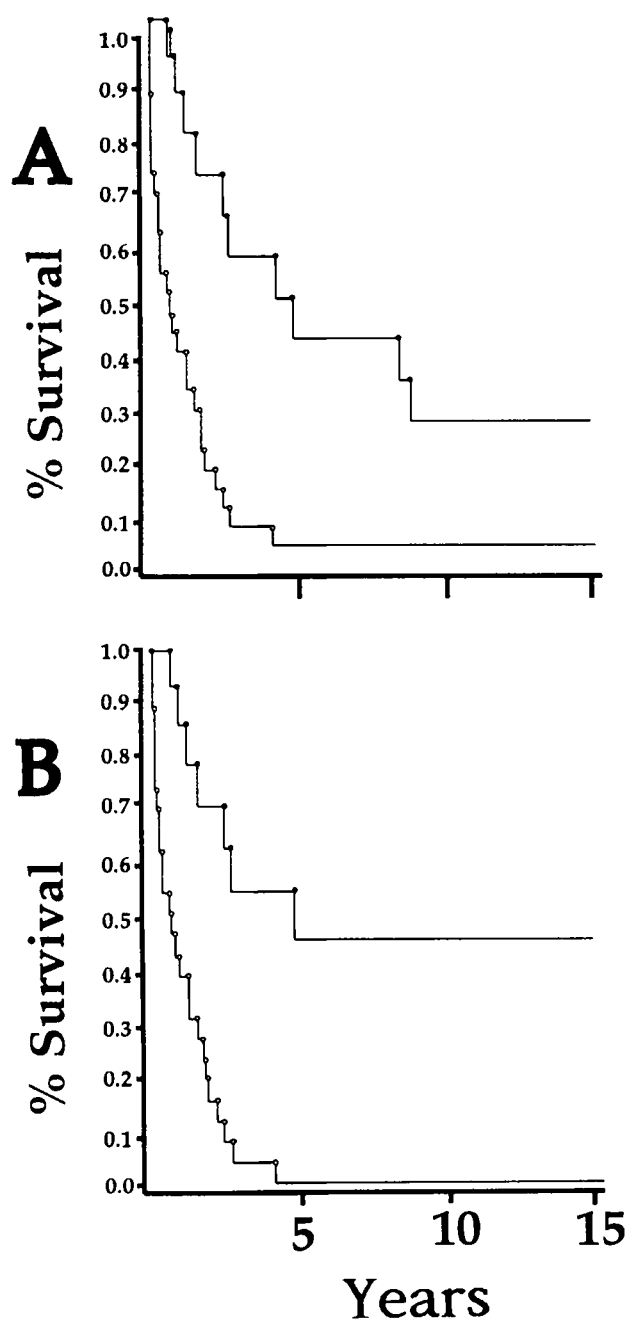


Fig. 4. Overall (A) and tumor-free survivals (B) of the 14 patients who required multiorgan resections and/or preoperative radiation to allow curative resection, compared to the 27 patients who underwent palliative operations. ●—●, multiorgan resection, preoperative radiation patients; —□—□, palliative operative patients.

The long-term survival of the 14 patients for whom an aggressive approach was employed for a potentially curative resection was especially gratifying. The overall 5- and 10-year survival rates of this group of patients were 39% and 23% (Fig. 4A), and the 10-year tumor-free survival was 45% (Fig. 4B). This was a highly significant increase in survival was compared to that of the 27 patients who underwent palliative procedures,

none of whom survived for 5 years ($P < 0.01$) (Fig. 4A,B; Table I).

CASE REPORT

A 57-year-old man was found at exploratory laparotomy to have a cecal carcinoma fixed to his right ureter, iliac vessels, and other retroperitoneal structures (Fig. 5A). At initial operation, the outer perimeter of the tumor was marked with clips, and an ileotransverse colostomy was performed. Also, the tumor-bearing right colon and the terminal ileum, proximal to the ileotransverse colostomy, were isolated from the remainder of the small and large intestine by suturing of the greater omentum to the distal terminal ileum from where it entered the tumor-bearing cecum to the ileotransverse colostomy, and to the anterior abdominal wall (Fig. 5B). After the patient's recovery from the initial laparotomy, the cancer was treated with 4,600 R of external-beam photon therapy. After the patient had rested for a month, he was re-explored. Upon re-exploration, the radiation-induced changes in the distal terminal ileum and tumor-bearing cecum were obvious when compared to the condition of the remainder of the small bowel, which had been shielded from the radiation by the omentum (Fig. 5C). An uneventful right colectomy was successfully performed at the second operation, and the tumor-bearing cecum was easily detached from all of the retroperitoneal structures, including the ureter (Fig. 5D). Unfortunately, this patient succumbed to progressive liver metastases 15 months after resection (Table II, patient #6).

DISCUSSION

There is little controversy that the aggressive resection of colorectal cancers invading other organs and those with isolated liver metastases, and the re-resection of anastomotic recurrences, will lead to long-term survival, and possibly cure, of a significant percentage of colorectal cancer patients [1-7]. Eleven percent (14/128) of the patients in our series required aggressive management, ranging from multiorgan resections and/or preoperative radiation treatment to be rendered tumor-free upon primary resection (Table II). The 10-year tumor-free survival of these 14 patients was 45%, and the 10-year overall survival was 23% (Fig. 4, Tables I, II). Given that all patients who underwent palliative procedures died of progressive disease (Fig. 1B), it seems clear that the use of an aggressive approach to render patients tumor-free at the time of primary resection will cure certain patients who would otherwise be lost to cancer (Fig. 4, Tables I, II).

Several studies have shown that certain colorectal cancers found to be fixed on initial exploration can be made resectable by radiotherapy in subsequent operations [8-13], as occurred for four of the six nonresectable cancers treated in this manner in the present series (Table

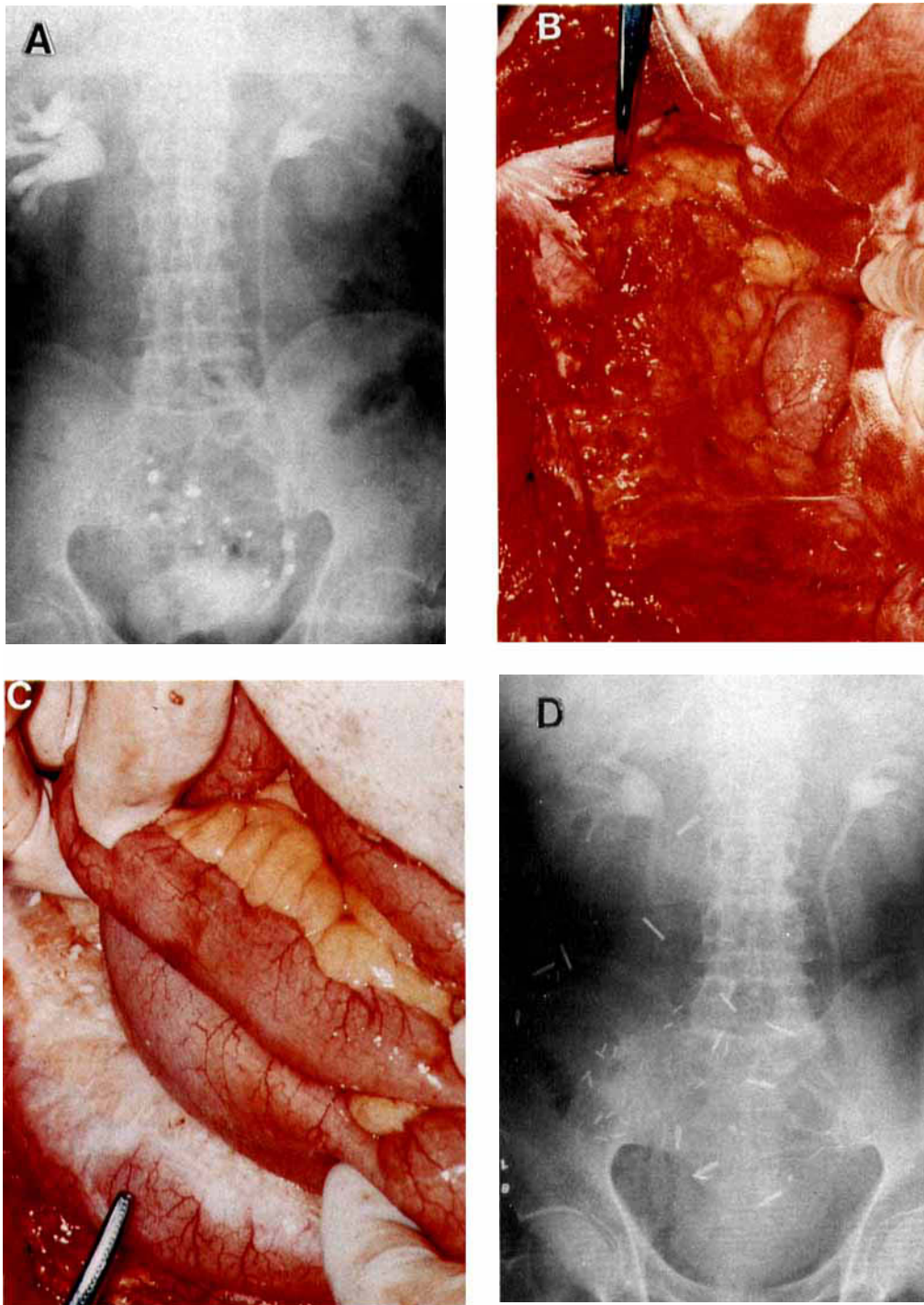


Fig. 5. Use of preoperative radiation, in combination with an "omental shield" which protected the normal small intestine from radiation damage, to allow the subsequent resection of a fixed cecal cancer. **A:** Preoperative IVP showing right hydronephrosis. **B:** View of the omental shield two months after initial laparotomy. The tip of the hemostat is on the anterior abdominal wall. Note how the omental shield partitions

the cecal cancer and terminal ileum (not shown) from the remainder of the small bowel. **C:** View of the irradiated terminal ileum (tip of the hemostat) and the remainder of the normal appearing small intestine, protected from radiation damage by the omental shield. **D:** Normal IVP 2 months after resection of the cancer.

II, patients #3–#6). The resectability of previously fixed tumors after radiotherapy may be due, in part at least, to radiation effects against the desmoplastic host response

elicited by the cancer. The long-term benefits of preoperative radiation for survival are less clear [14]. Nevertheless, the probable cure of two patients with fixed cancers that

were treated in this way (Table II, patients #3 and #4) would seem to establish a survival benefit for this approach. Thus, the results for this, and other series [8–14], clearly suggest that, whenever a surgeon encounters fixed, nonresectable colorectal cancer during the initial exploration of a patient without metastatic disease, that the tumor should be marked with clips, the patient closed, and a course of at least 4,500 R of external-beam radiotherapy administered. One month after completion of radiotherapy, these patients should be re-explored and an attempt made at curative resection (Table II). The use of omental shields or Vicryl mesh to isolate the normal intestine from the tumor-bearing segment of bowel so that it is outside the radiation field [39,47] may have considerable value in preventing radiation enteritis (Fig. 5).

The possible value of radical lymphadenectomies for colorectal cancer, however, cannot be assessed so clearly. The placement of a “high tie” on the inferior mesenteric artery and performing aortic lymphadenectomies from the duodenum down to, and past, the aortic bifurcation for mid- and low-rectal cancers probably has not gained enough support in retrospective studies to merit a randomized trial. Such aortic lymphadenectomies for rectal lesions are associated with genitourinary complications [40,48,49], although these complications may be lessened with nerve sparing operations [22,50]. Nevertheless, the St. Mark’s series shows no improvement in survival for rectosigmoid cancer patients after such extensive lymph node dissections, when compared to identically staged patients undergoing lesser procedures [37,38]. Other, smaller series have given similarly disappointing results with radical aortic lymphadenectomies performed for mid- and low-rectal cancers [24,35]. Thus, although certain authors believe that there may be a possible therapeutic benefit of aortic lymphadenectomies for such tumors [19,22,25–28,33,34], this benefit, if any, may be of insufficient magnitude to be detected in a reasonably sized, randomized trial. Such high aortic lymphadenectomies were not carried out in this series for mid- and low-rectal cancers.

Several retrospective reports do suggest however, that wide removal of the lymph node basins adjacent to colorectal cancers may confer a considerable survival benefit [15–22,34,39,48–59], although others dispute this claim [5,24,38,60]. In the present study, there was a suggestion of an improved overall 5-year survival for the Dukes’ stage B and C patients who had scrupulous clearance of the primary nodal basins adjacent to the cancer, when compared to similarly staged patients undergoing standard resection ($P < 0.04$) (Table I, Fig. 2A). The tumor-free survival rates of these patients were also slightly higher after radical resection (Fig. 2B), although not significantly so at either the 5- or 10-year intervals (Table I).

It is not clear from this data set whether the radical lymphadenectomies really conferred a significant survival benefit to the colorectal cancer patients, or whether this

apparent benefit of the “radical” operation (Fig. 2A) was simply due to the inadvertent selection, for the radical procedure, of patients who were “more fit.”

The majority of published retrospective studies seem currently to favor the performance of wide lateral lymphatic dissections for rectal cancers [22,34,39,48–59], although other reports dispute the benefits of such procedures [37,38,60]. In our series, an improvement in overall survival was found for the rectosigmoid cancer patients undergoing a “radical resection” which entailed a wide lateral lymphatic dissection ($P < 0.05$) (Fig. 3A, Table I). Also, the tumor-free survivals of the radically resected patients were higher than those of the patients undergoing standard resections (Fig. 3B), although the P -values separating the two curves were only < 0.17 at 5 years and 0.09 at 10 years (Table I).

The rectosigmoid cancer patients in this series who were undergoing radical and standard resections were well matched with respect to tumor stage and patient age. It is possible that chance, unrecognized selective factors, or statistical artifacts secondary to subset analysis can provide the explanation for the apparent survival benefit of radical resection observed for these patients. However, these results are also consistent with the possibility that the wide anatomic resection of tumor-adjacent mesenteric lymph nodes indeed has a therapeutic benefit for rectosigmoid cancer patients. We, together with others [40], believe that controlled trials are needed to settle this important issue.

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